

REMARKS

Claims 27 and 29-37 are currently pending in this application. Claims 12-24, 26 and 28 have been canceled without prejudice. Claim 27 has been amended to recite "a pharmacologically acceptable salt thereof" instead of "a pharmacologically acceptable salt, solvate, hydrate or formulation thereof." Claim 29 has been amended to recite "breast cancer or epidermoid cancer." Claim 30 has been amended to correct its claim dependency. Claims 31 to 36 are new and are directed to various definitions for the variable groups found in previously presented and now canceled claims. Additional support can be found throughout the specification. Claim 37 is new and is directed to a method of treating a patient suffering from or susceptible to ovarian cancer, lung cancer, cervix carcinoma, cancer of the bladder or leukemia. Support for these new claims and claim amendments can be found throughout the specification as originally filed, for example, at pages 1 and 7-8 and the original claims of the application. No new matter has been added by these amendments.

Amendment of the claims should not be construed as acquiescence to any of the rejections set forth in the Office Action and was done solely to expedite prosecution of the application. Applicant respectfully reserves the right to pursue the claims as originally filed or similar claims as well as any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections to this application in view of the amendments and remarks herewith, are respectfully requested, as the application is in condition for allowance.

Rejections under 35 U.S.C. 112, first paragraph

Claims 12 – 24 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement, in particular to the definition of A. Without conceding the validity of the Examiner's rejections, Claims 12-24 have been canceled without prejudice. As such, the Examiner's rejection is now moot.

Claims 12-24, and 26-30 also stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement, particularly with respect to the making of a solvates in the isolatable or solid form. As stated above, Claims 12-24 and 26 have been canceled without prejudice. As such, the rejection with respect to those claims is now moot. With respect to claims 27-30 and new claims 31-37, while Applicants strongly disagree with the Examiner's allegation, and solely for the purpose of advancing prosecution, claim 27 has been amended to recite only "a pharmacologically acceptable salt thereof" instead of "a pharmacologically acceptable salt, solvate, hydrate or formulation thereof." No new matter has been added by this amendment.

Finally, Claims 22, 23, 29 and 30 also stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner states that the specification is "enabling for treating some cancers, [but] does not reasonable provide enablement for all cancers." As stated above, Claims 22 and 23 have been canceled without prejudice. As such, the rejection with respect to those claims is now moot.

With respect to Claims 29, 30, and new Claim 37 while Applicants strongly disagree with the Examiner's allegation, Claim 29 has been amended to relate to breast cancer and epidemoid cancer. Support for this amendment can be found throughout the specification, particularly in the Nicolaou (*Angew. Chem. Int. Ed.* 1998, 37, 2014-2045) and Florsheimer (*Expert Opin. Ther. Patents* 2001, 11, 951-968) references cited therein. New Claim 37 relates to a method of treating a patient suffering from or

susceptible to ovarian cancer, lung cancer, prostate cancer, cervix carcinoma, cancer of the bladder or leukemia. Support for this claim can also be found in the Nicolaou and Florsheimer references. Additional support can be found in the Feyen (*Agnew. Chem. Int. Ed.*, 2006, 45, 1-6) and Hofle (*Anticancer Agents from Natural Products*, Chapter 21, Craig *et al.* ed., Taylor and Francis, Boca Raton, 2005) references enclosed herewith.

Furthermore, Applicants respectfully submit herewith a declaration of Dr. Wolfgang Richter which demonstrates, by means of published experimental data, that "replacing the carbonyl function at the 5-position of an epothilone derivative by a sulfide or a sulfone function results in an epothilone derivative having similar activity against certain cancer cell lines." While Dr. Richter references two publications directed to breast cancer (human cell line MCF-7) and epidermoid cancer (human cell line kb-31), Applicants submit that this experimental data demonstrates a correlation between the instantly claimed compounds and methods and, *at a minimum*, the cancer cell lines disclosed in the declaration as well as those of the Nicolaou and Florsheimer references. A similar correlation would be readily extrapolated from the Feyen and Hofle references by one of ordinary skill in the art. As such, Applicants assert that the instantly claimed methods are fully enabled.

Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 112, First Paragraph be reconsidered and withdrawn.

Rejections under 35 U.S.C. §103 (a)

Claim 12-23 and 26-30 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over Nicolaou in view of Patani (*Chem. Rev.* 1996, 3147-3176). As stated above, Claims 12-24 and 26 have been canceled without prejudice. As such, the rejection with respect to those claims is now moot. With respect to claims 27-30 and new claims 31-37, Applicants respectfully traverse.

To properly determine a *prima facie* case of obviousness, the Examiner “must step backward in time and into the shoes worn by the hypothetical ‘person of ordinary skill in the art’ when the invention was unknown and just before it was made.” M.P.E.P § 2142. This is important as “impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art.” *Id.* Four factual inquiries must be made: first, a determination of the scope and contents of the prior art; second, a determination of the differences between the prior art and the claims in issue; third, a determination of level of ordinary skill in the pertinent art; and fourth, an evaluation of evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Three criteria may be helpful in determining whether claimed subject matter is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). “Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious.” *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

It has been acknowledged that “Nicolaou et al. do not teach a thioether or a SO₂ in place of the carbonyl next to the gem-dimethyl of the epothilone ring.” The Examiner relies on Patani for the alleged teaching that “carbonyl can be replaced by S, SO, SO₂ if the position is not essential to the function of the molecule.”

As discussed in Applicants’ prior response, Patani is merely a background article and provides no motivation to modify the Nicolaou et al. document as has been proposed.

Applicants respectfully submit herewith a declaration of Prof. Dr. Ludger Wessjohann. Dr. Wessjohann states that Patani discusses a series of benzophenone dicarboxilic acids as potential inhibitors of LTB4 and concludes that the replacement of the carbonyl with either a thioester, a sulfoxide or a sulfone is not critically involved in LTB4 receptor binding. (Wessjohann Declaration ¶ 4). As such, one of ordinary skill in the art, upon reading Patani would conclude that one would expect major changes in biological activity if CO is replaced by sulfur or SO₂ in a critical part of a molecule, but no significant changes in a non-critical part of a molecule. (Wessjohann Declaration ¶ 5). In other words, and as the Examiner characterized Patani, “carbonyl can be replaced by S, SO, SO₂ ***if the position is not essential to the function of the molecule***” (emphasis added).

Nicolaou teaches that ***a loss of activity*** was observed when the C5 ketone was reduced or when the C5 substituent was removed (Nicolaou, Page 2040). Dr. Wessjohann states that “this clearly shows, that the CO-moiety at the C5 position is of great importance for the activity of epothilone derivatives” and that “a person of ordinary skill would... determine that ***this position is essential for the biological activity*** of the compound.” (Wessjohann Declaration ¶ 6, emphasis added)

As such, one of ordinary skill in the art would have clearly lacked any motivation to combine Nicolaou with Patani as the teaching of Patani is only potentially relevant if the position is ***not essential*** to the function of the molecule. Furthermore, one of ordinary skill in the art would have lacked any expectation of success in modifying the compounds of Nicolaou with a sulfur or SO₂ as allegedly suggested by Patani without greatly altering the biological activity.

Indeed “if at C5 of an epothilone derivative, CO is replaced by sulfur or SO₂, a person of ordinary skill in the art would expect that this replacement will have a great influence on the biological activity of the corresponding derivative. Consequently, a person of ordinary skill in the art could not expect that the molecules of the present invention show similar activities when compared with compounds carrying a CO group at C5.” (Wessjohann Declaration ¶ 7).

Similarly, Dr. Wessjohann points out that "due to the different binding angles and size the person skilled in the art would expect that the replacement of CO by sulfur or SO₂ has a great influence on the conformation of a macrocycle and therefore, the person skilled in the art would expect that this also has a great influence on the biological activity of the corresponding derivative. [However, it]... is apparent from the data given in the enclosed declaration by Dr. Wolfgang Richter, this is not the case in the epothilone derivatives of the present invention." (Wessjohann Declaration ¶ 8) Also, Dr. Wessjohann notes "that in a R-CO-R molecule, all groups lie within one plane; whereas in a R-SO₂-R molecule, the oxygen is positioned above and below the plane created by the R-S-R group. Therefore, a person of ordinary skill in the art would expect that the activity of epothilone derivatives wherein the CO moiety at position C5 is replaced by a SO₂ moiety, and the activity of the resulting derivatives would rather be comparable with the activity of a derivative carrying an OH group at C5. As discussed above, Nicolaou teaches that this derivative shows a loss of activity." (Wessjohann Declaration ¶ 9).

In sum, since the epothilone CO is shown to be a critical part of the molecule by Nicolaou and any modification of CO by sulfur or SO₂ at a critical part of the molecule would be expected to result in major changes in biological activity according to Patani, one of ordinary skill in the art would have had no expectation of success in modifying the CO of the compounds of Nicolaou with sulfur or SO₂ without potentially sacrificing the beneficial biological properties of the compounds of Nicolaou.

The compounds of the instant invention, however, unexpectedly and surprisingly show similar beneficial activity with respect to certain cancer cell lines as known epotholones despite replacement of CO by sulfur or SO₂ at a critical part of the molecule.

As such, Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 103, be withdrawn.

Double Patenting Rejections

Claims 12-23 and 26-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 11 of United States Patent Application Serial No. 10/520,769 in view of Patani et al. As stated above, Claims 12-23 and 26 have been canceled without prejudice. As such, the rejection with respect to those claims is now moot.

With respect to claims 27-30 and new claims 31-37, as discussed above, Patani et al. is merely a background document and provides no suggestion to modify the cited copending application claims in a manner sufficient to sustain the instant rejection.

Nevertheless, as it remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable, any statement regarding the provisional rejection made would be premature. Moreover, this provisional rejection can be properly withdrawn if it is the only outstanding rejection in the case. See Section 804 of the Manual of Patenting Examining Procedure.

Therefore, Applicants respectfully request that this rejection be held in abeyance until claimed subject matter is deemed allowable in the application.

CONCLUSION

In view of the amendments and remarks made herein, Applicant submits that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. If a telephone conference with Applicant's representative would be helpful in expediting prosecution of the application, Applicant invites the Examiner to contact the undersigned at the telephone number indicated below.

Applicant believes that no additional fees, other than the fee for the three-month extension of time, are required in connection with this paper. Nevertheless, Applicant authorizes the Director to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 04-1105, under Order No. 63419(52171) .

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Respectfully submitted,

By _____ /Nicholas J. DiCeglie, Jr./

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